Appln No.: 09/913,325
Amendment Dated: April 29, 2005
Reply to Office Action of October 29, 2004

REMARKS/ARGUMENTS

This is in response to the Office Action mailed October 29, 2004 for the above-captioned application. Reconsideration and further examination are respectfully requested.

Applicants request an extension of time sufficient to make this paper timely and enclose the fee. The Commissioner is authorized to charge any additional fees or credit any overpayment to Deposit Account No. 15-0610.

The Examiner objected to the Abstract because it contains more than 150 words. A shortened abstract has been provided.

The Examiner objected to claims 19 and 20. Claims 19, 22 and 23 have been amended such that claims 19-23 are dependent on original claim 18. No new matter has been added. This amendment also addresses the rejection of claims 21-23 under 35 USC § 112, second paragraph.

The Examiner rejected claims 1, 2, 6-8, 12-25, 30-32 and 34 under 35 USC § 112, first paragraph, asserting that these claims are not supported by an adequate written description. Applicants respectfully disagree.

As the Examiner has stated, case law establishes that compliance with the written description requirement requires that the specification "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, [the inventor] had possession of *the invention*. The invention is, for purposes of the written description inquiry, whatever is now claimed." *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117.

In the present case, the invention is defined in four sets of claims:

(1) delaying progression of prostatic tumor cells to an androgen- independent state (claims 1-5)

(2) treating prostate cancer in an individual suffering from prostate cancer (claims 6-17, and 29-34)

(3) for enhancing the chemo- or radiation sensitivity of cancer cells (claims 18-23)

(4) for delaying of progression of a population of prostatic tumor cells from a state in which living prostatic tumor cells are androgen-sensitive to a state in which living tumor cells are androgen independent (claims 24-28)

Thus the invention for which written description must be established is these methods.

The Examiner acknowledges that "the specification teaches on page 3 that the inventors have discovered that antisense therapy that reduces expression of TRPM-2 provides therapeutic benefits in the treatment of cancer, and that TRPM-2 antisense oligonucleotides are effective at delaying onset on androgen independence in prostatic tumors in vivo." (Office Action Page 6). Applicants respectfully submit that this acknowledgment, and the teachings on which it is based show that Applicants did have possession of the invention as claimed.

In presenting the written description rejection, the Examiner has reproduced a substantial amount of text from cases, but has not really applied this case law to the issues presented in the present case. For example, the citation of *Univ. of Rochester v. G.D. Searle*, is not directly applicable to the present case, because in that case no molecules capable of use in the claimed method were described in the application. That plainly is not the case here, since Applicants disclose several antisense sequences specific for TRPM-2, most of which are human sequences.

The Examiner continues by citing additional cases and arguing that the written description requirement is not met because the skilled artisan cannot envision the detailed structure of the encompassed anti-TRPM2 antisense sequences.[1] The cases on which the Examiner relies, however, deal with compositions, not method claims. Thus, these arguments do not look at the invention as claimed, but at the possibility (or even probability) that additional antisense species may exist and may be discovered by others in the future. These future inventors may be entitled to patent protection on their individual compositon discoveries, but it is improper to limit Applicants' method claims at this time such that these future inventors would be free to appropriate Applicants' invention and by using their later discovered compounds in Applicants' invention.

Applicants would further note that the Examiner's argument appears to be inconsistent with the Training Materials on Written Description that are posted on the USPTO web site (http://www.uspto.gov/web/menu/written.pdf) and in particular with Example 15, a copy of which is attached hereto. This Example concludes that a disclosure of a full length sequence and describes the known gene-walking technique provides an adequate description for a claim broadly reciting inhibitory oligonucleotides, even though no species other than the full length sequence are disclosed. While Applicants appreciate that this training materials is not binding authority, it is available through the USPTO web site and following the guidance of such a document would indicate that the inventions of the present method claims are more than

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[1] For convenience and clarity, the assertions concerning sufficiency of written description of other inhibitors is dealt with separately.

sufficiently described, particularly since the claims are directed to methods, and not to compositions.

The Examiner also objected to claims which mention antisense to Bcl-2 and other apoptotic proteins because only one Bcl-2 antisense sequence was disclosed. Applicants submit that this type of rejection applied to a dependent claim is inappropriate and could even be described as ill-considered. Because the independent claims are drafted in "comprising" language, the claims encompass methods that include steps that are not disclosed. Applicants has disclosed as a feature of their invention, that it may be used in combination with other antisense therapies and provided as one specific example a sequence from the art that was used in examples to establish proof of principle. Surely the written description requirement is not intended to create a requirement of encyclopedic recounting of all known sequences that might be used in the invention when a generic description is provided.

Independent claims 6 and 18 encompass the use of compositions that inhibit expression of TRPM-2 that are not limited to antisense compositions. Here, the Examiner asserts that this claim is overly broad because these compositions cannot be envisaged. As previously discussed, however, these are not composition claims but method claims. Nothing in the specification suggests that there is anything critical about the type of agent used to reduce expression, or that other types of agents could not be used. Further, the application as filed contained the broader claim, indicating that Applicants recognized as part of their invention, and had possession of the idea and the invention of using any agent at all that accomplished the stated purpose.

For these reasons, Applicants submit that the written description rejection is in error and should be withdrawn.

The Examiner also rejected claims 1, 2, 6-8, 12-25, 30, 32 and 34 under 35 USC § 112, first paragraph, as lacking enablement. The Examiner asserts that enablement is only provided for use of TRPM-2 antisense *in vitro* or *in vivo* in mice, and not in combination with other agents or in other species. Applicants respectfully disagree.

On Page 17 of the office action, the Examiner states that "in order to practice the claimed invention *in vivo* in all organisms a number of variables would have to be optimized." As a first matter, Applicants point out that enablement does not require optimization. It merely requires that some level of activity is obtained. Thus, to the extent the rejection is based on a requirement for a higher standard, it is in error and should be withdrawn.

The Examine further lists five specific variables. First, the Examiner states that experimentation would be required to determine suitable antisense sequences. It is pointed out, however, that Applicants have disclosed specific sequences that bind to human TRPM-2, and

provided guidance where in the sequence (translation initiation or termination sites) and by analogy to the location of the human sequences where antisense can be derived for other species.

Second, the Examiner says that the form of the nucleotide, for example, whether to use a modified oligonucleotide with one or more backbone, sugar or base modifications would be the subject of experimentation. Options for modification are disclosed (for example phosphorothioate oligonucleotides) and optimization is not required. That there may be some other later-developed modification that is superior is not relevant to enablement.

Third, the Examiner states that mode of delivery must be considered so that the antisense reaches the targeted cell. It is pointed out that in the *in vivo* mouse experiment, the antisense was administered intraperitoneally yet reduction of expression in the implanted human tumors was observed. Thus, the basis for specific requirements for administration is not based on the application.

Fourth, the Examiner argues that experimentation would be needed to determine the specific amount of antisense needed. As noted in the specification, such determinations are a routine part of clinical trials and cannot be deemed undue experimentation.

Fifth, the Examiner states that one must ensure that antisense remains viable in the cell for a period of time sufficient to observe a "measurable and significant therapeutic effect." Applicants again remind the Examiner that enablement does not require a therapeutic effect of any particular level of significance, beyond one that is observable. Persons who have suffered the side effects of chemotherapy and radiation might well argue, however, that any ability to increase the effectiveness of the treatment, and thereby allow reduction in the amount of agent/radiation used, would be significant. It should further be noted that chemotherapy and radiation are short duration treatments. Thus, the period of time over which reduction in TRPM-2 needs to occur is also short. The Examiner has not addressed why this would appear as a particular challenge, given the data in the application.

The Examiner acknowledges that "optimization of any single one of these steps may be routine", but argues that "when taken together the amount of experimentation required becomes such that one of skill in the art could not practice the invention" without undue experimentation. Applicants submit that this argument is not consistent with the specification.

As further evidence of enablement, Applicants enclose a copy of a declaration submitted in a related case, Serial No. 09/967,726 containing results from an on-going clinical trial in humans. This trial was designed to test for reduction in TRPM-2 levels, and for toxicity, rather than to achieve a therapeutic effect. As such, reductions in chemotherapy levels were not made. The desired reduction in TRPM-2 levels was observed, and toxicity was limited. Furthermore,

despite the nature of the trial design, significantly improved biochemical results (reduced tumor marker levels) were achieved in two patients with ovarian cancer and two patients with prostate cancer. Standard protocols were used to select the amount of material administered. The antisense was a modified form of Seq. ID No. 4. This further evidence refutes the Examiner's rejection for lack of enablement.

For these reasons, Applicants submit that the rejection for lack of enablement should be withdrawn.

The Examiner rejected claims 18 as claiming the same invention as claim 1 of copending application 09/967,726. Claim 1 of the '726 application was amended in an amendment filed by facsimle on April 18, 2005. Thus, this rejection is believed to be moot.

The Examiner provisionally rejected claims 1, 3, 6, 9, 14, 15, 18, 21, 24, 26, 29 and 30 for obviousness type double patenting in view of claims 2-4, 6, 10 and 11 of Serial No. 10/080,794. The Examiner asserts that double-patenting is an issue because the subject matter of claims of the '794 application are encompassed within the scope of the present claims, i.e, because the present application is directed to a genus while the '794 application is directed to a species within that genus. This, however, is not the appropriate standard for a rejection for obviousness-type double patenting. The Examiner must look at whether the claims are obvious variants of one another, applying a standard that is substantially similar to that applied in assessing patentability under § 103. This has not been done.

The claims of the '794 application were deemed patentable over the earlier disclosure of the Seq ID No: 4 sequence without the specific modification, and the issue fee has been paid. Because the present application is the earlier application, a two-way test for obviousness must be applied. Since the species claims of the later application are patentably distinct (as reflected by the allowance), no obviousness-type double patenting rejection is appropriate in either case.

The Examiner provisionally rejected claims 1-11, 18 and 24-34 for obviousness-type double patenting over claims 1-3 and 9 of Application Serial No. 10/646,391. The claims of the '391 application relate to treatment of melanoma. The rejected claims of this application relate to prostate cancer or to enhancing sensitivity to radiation or chemotherapy. The Examiner chooses to ignore these differences, relying on the fact that the method step is the same. The Examiner has provided no evidence that knowledge that of the one invention provides a suggestion of the other, or even that there is an overlap in claimed subject matter. Thus, the rejection is in error and should be withdrawn.

Claims 1-11, 18 and 24-34 are provisionally rejected for obviousness-type double patenting over claims 1-3 and 6-8 of Application Serial No. 10/828,394. Again, the methods are

different, even though the therapeutic agent is the same, and the Examiner has provided no evidence that the claimed subject matter even overlaps. The Examiner may not consider only the active step, but must make a full obviousness determination and substatiate it with reasoned argument. This has not been done and the rejection should therefore be withdrawn.

Claims 1-11, 18 and 24-28 are also provisionally rejected for obviousness type double patenting over claims 1-3 and 6-8 of Application Serial No. 10/828,395. Here, the claims of the cited application do not even relate to cancer treatment, and thus there is no apparent overlap in the subject matter of the claims. Thus, there is no basis for an obviousness-type double patenting rejection because the two applications do not seek to patent the same things.

The Examiner has also made statements, although not rejections, that the claims of the present application are not patentably distinct from the claims of other applications that parallel the double-patenting rejections. For the Examiner's information, however, Applicants note that all of the cited applications and this application were the subject of a common obligation to assign to The University of British Columbia at the time the inventions claimed therein were made. Thus, these statements are believed to be irrelevant to the status of this application.

The Examiner rejected claims 1, 2, 4, 6-8, 10, 18-20, 22, 24, 25 and 27 as anticipated by or obvious over Sensibar. Applicants respectfully traverse this rejection. Sensibar discloses an antisense oligonucleotide that is effective to reduce expression of TRPM-2 in LNCaP prostate cancer cells. The Examiner acknowledges that Sensibar is silent as to delaying progression of prostate cancer cells to androgen independence or enhacning chemo or radiation sensitivity but says that this is irrelevant because is would be expected to have this result based on Applicants teaching. Applicants will assume this is a rejection based on an inherency argument rather than an improper reliance of their own teachings to support the rejection. However, inherency arguments are more appropriate in the context of the composition claims, where a propert of the composition is recited. No such composition claims are present in the rejected claims.

Sensibar discloses antisense specific to TRPM-2, but does not teach that TRPM-2 is itself of any significance in cancer or provide a basis to imagine that inhibition of TRPM-2 would provide any therapeutic benefit. Sensibar does not teach or suggest that TRPM-2 antisense has any anticancer utility on its own. All that Sensibar teaches is an antisense that reduces expression of TRPM-2 in a LNCaP cell lines that has been modified to overexpress TRPM-2, and that this overexpression could prevent cell death induced by tumor necrosis factor-α. Sensibar certainly does not teach use of TRPM-2 antisense as a therapeutic that is administered to a cancer patient, as required in rejected claims 6-8, 10, 18-20 and 22, and thus cannot be deemed anticipatory. Further, the Examiner has failed to explain how such a treatment method would be considered obvious in the absence of any teaching or suggestion of therapeutic utility.

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Accordingly, Applicants submit that the anticipation rejection is in error and should be withdrawn.

For these reasons, this application is now considered to be in condition for allowance and such action is earnestly solicited.

Respectfully submitted,

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Enclosures:

Petition for Extension of Time
Credit Card Payment Form
Copy of Declaration from 09/967,726 (UBC.P-022)
Example 15 from Training Material

Example 15: Antisense

Specification: The specification discloses a messenger RNA sequence, SEQ ID NO: 1, which encodes human growth hormone. The specification states that the invention includes antisense molecules that inhibit the production of human growth hormone. The specification describes an art-recognized method of screening for antisense molecules that is called "gene walking." Gene walking is said to involve obtaining antisense oligonucleotides that are complementary to the target sequence.

Claim:

An antisense oligonucleotide complementary to a messenger RNA having SEQ ID NO: 1 and encoding human growth hormone, wherein said oligonucleotide inhibits the production of human growth hormone.

Analysis:

A review of the full content of the specification indicates that the complement of SEQ ID NO: 1 is essential to the operation of the claimed invention. The general knowledge in the art is that any full-length complement of a target mRNA inhibits the function of the mRNA and is therefore an antisense oligonucleotide. Thus, one of skill in the art would view applicant's disclosure of a coding sequence, with the statement that the invention includes antisense oligonucleotides, as an implicit disclosure that the full-length complement of SEQ ID NO: 1 is an antisense oligonucleotide.

It is generally accepted in the art that oligonucleotides complementary to a messenger RNA, including fragments of the full-length complement, have antisense activity when they match accessible regions on the target mRNA. Generally, the closer the complementary fragment is to full length, the greater the likelihood it will have antisense activity. In addition, oligos that retain complementarity to the Shine-Delgarno sequence usually have antisense activity.

The claim is drawn to the genus of antisense molecules that inhibit the production of human growth hormone encoded by SEQ ID NO: 1. There is a single species described with a complete structure, i.e., the full-length complement of SEQ ID NO: 1. In addition to the full-length complement, the genus includes fragments of the complement that retain antisense activity.

The procedures for making oligonucleotide fragments of the SEQ ID NO: 1 complement are conventional, e.g., any specified fragment can be ordered from a commercial synthesizing service. The procedures for screening for antisense activity are also conventional, and the specification describes the assay needed to do gene walking. The experience accumulated in the art with gene walking is that numerous regions of a target are accessible, that these regions are identified routinely, and that antisense oligonucleotides are complementary to these accessible regions. The full-length complement and longer fragments match multiple accessible regions; shorter fragments match fewer accessible regions.

When considering the distinguishing characteristics of the claimed invention, the sequence provided in the specification defines and limits the

structure of any effective antisense molecules. The specification also teaches the functional characteristics of the claimed invention as well as a routine art recognized method of making and screening for the claimed invention. Considering the specification's disclosure of:

(1) the sequence (SEQ ID NO: 1) which defines and limits the structure of any effective antisense molecules such that one skilled in the art would be able to immediately envisage members of the genus embraced by the claim, and

(2) the functional characteristics of the claimed invention as well as a routine art-recognized method of screening for antisense molecules which provide further distinguishing characteristics of the claimed invention, along with

(3) the general level of knowledge and skill in the art,

one skilled in the art would conclude that applicant was in possession of the invention.

Conclusion: The claimed invention is adequately described.